editorial

Future directions in therapy for chronic kidney disease

ALM de Francisco

Nephrology Department. Valdecilla University Hospital. Santander, Spain

Nefrologia 2010;30(1):1-9

The increasing prevalence of chronic kidney disease is well known, as it is a fact that recorded data in all countries show continuing growth in the number of patients that need substitutive treatment for their renal function. The consequences from the social and economic viewpoint are very significant and we cannot be happy with morbidity and mortality rates in terminal stage renal patients that continue to be unacceptably high.[1,2] There are different reasons for such high mortality rates, amongst them significant increase in the age of patients undergoing treatment, restoration with haemodialysis and peritoneal dialysis of only 15 to 20ml/min of kidney function, and a significant associated co-morbidity. Despite the progress made in haemodialysis (membrane biocompatibility, high-flow membranes, increase frequency in sessions, water quality control, among others) and in peritoneal dialysis (infection risk reduction, introduction of a dialysis machine, etc.) no clear improvement has been shown in the evolution of patients.

Therefore, if so little improvement has been made after so many years, what is in store for the future for renal function replacement? This article aims at highlighting which are the future possibilities to face renal insufficiency, by substitutive techniques such as haemodialysis, peritoneal dialysis or kidney transplant (or creation of new organs), as well as the possibility of regression of chronic kidney disease before total loss of renal function.

HAEMODIALYSIS: PORTABLE OR IMPLANTABLE KIDNEYS

As it has been expressed, the situation of patients undergoing haemodialysis means a great sacrifice, overall, both for the patients themselves and their families, especially because of their bad quality of life and the need to move over to the dialysis centre three or more times per week. Furthermore, a high mortality rate (similar to metastatic breast cancer, colon or prostate cancer) forces to move on toward applying different techniques.

The fact that there is evidence of improvement with frequent and prolonged dialysis in quality of life and anaemia control, hypertension control, hospitalisations, medication reduction (i.e. anti-hypertensive or phosphate binders), appetite improvement, volume control improvement, morbidity and mortality reduction, etc., it all leads research toward types of techniques with continous treatment.

It is true that continuous ambulatory peritoneal technique could somehow come closer, as in fact it does, to continous treatment. It has been used for many years in many centres. However, the percentage of patients does not extend beyond 10-15% of those undergoing dialysis and, besides, there is a significant decline as time passes due to loss of ultrafiltration capacity or peritoneum diffusion, which is insufficient in many cases when the residual renal function disappears.

The requirements for new technologies in dialysis are, therefore, based on the following objectives:

1. Continuous function.
2. Elimination of molecular weight solutes similar to kidney function.
3. Elimination of water and solutes according to patient's needs.
4. Biocompatibility.
5. Portable, or even better, implantable.
6. Low cost.
7. Safety.

There are currently four possible models that could reach these objectives in the future: HNF (Human Nephron Filter), micro-fluid techniques, WAK (Wearable Artificial Kidney) and RAD (Bioartificial Renal Assist Device).

Correspondence: ÁLM de Francisco
Servicio de Nefrología.
Hospital Universitario Valdecilla. Santander. Spain.
martinal@unican.es

Human Nephron Filter (HNF)

Nisenson et al.[3,4] have proposed this model as an innovation in the treatment of renal insufficiency. HNF consists in two membranes that work in series within a receptor. The first membrane is called membrane G and it is similar to the glomerular membrane. It uses convective transport to generate plasma ultrafiltrate containing solutes approaching albumin molecular weight. The second membrane is called membrane T and it reproduces the tubule functions. It is molecularly engineered and consists of pores of different sizes and angles, each one of which allows a solute dependent selection, so that between solutes with the same molecular weight some are discarded and some are not. Pores with similar radius are designed for different selecting transportation properties. Ultrafiltrate resulting from blood making contact with membrane G contains wanted and unwanted solutes. When passing onto membrane T, this membrane rejects the unwanted solutes and allows the wanted solutes to go through, as each one of its pores discriminates according to its design what is to be kept and what to be eliminated. Blood flows at 100ml/min and no dialysing is used in this system.

There are important differences between membranes built by molecular engineering and standard polymer membranes. The former have a pre-determined size number of pores with specific interactions that allow transport selection. On the contrary, standard polymer membranes are much thicker resulting in non-selective solute transport, and their pore sizes vary greatly.

HNF may be portable, with the filter including membranes G and T and, also, with a belt carrying a high capacity battery and a waste bag with conventional vascular access or using different varieties of percutaneous access.

Membrane-free dialysis: micro-fluid techniques

Micro-fluid technology is based upon the parallel flow of two currents in one single channel. Two liquids (for example, blood and a PBS solution) circulate in a laminar manner, one next to the other without any turbulent mix and without being physically separated by a membrane. Under these conditions diffusion takes place; so that small particles (such as ions, small proteins, numerous molecules and many drugs) tend to diffuse rapidly from the higher concentration side onto the smaller concentration side, whereas larger molecules and particles, such as cells, tend to diffuse minimally. Leonard et al.[5,6] have put forward that micro-fluid technique is a science of possible application in the field of haemodialysis. There are currently prototypes of filters H that by simple gravity aid diffusion of small molecules, from blood to dialysis liquid, and it is possible that in the future building multiple micro-fluid chambers may be clinically applied, and that these allow miniaturization of an artificial kidney and that creating a portable kidney may be achieved. However, there is still significant time ahead for research to resolve problems such as ultra-filtration and albumin retention.

Wearable Artificial Kidney (WAK)

Gura et al.[7,8] developed a portable haemodialysis device based on a 0.6m^2 polysulfone high-flow dialyser. This consists of a circuit where the blood compartment through the arterial line sends blood to the dialyser and back to the patient, and a dialysing compartment where the dialysis liquid enters the dialyser and it is then circulated by a series of sorbents where it is regenerated and bicarbonate is added to it. There is also a series of miniature pumps that regulate anti-coagulation and ultra-filtration.

Davenport et al.[9] studied 8 patients on haemodialysis, whom received and carried that portable kidney for 4-8 hours. These patients received heparin for anticoagulation. No significant cardiovascular changes or adverse effects appeared. Mean blood flow was 58ml/min, with a dialysed flow of 47ml/min and mean creatinine clearance of 20.7ml/min. Coagulation of circuit occurred in 2 cases when heparin dosing was reduced.

It is evident that the prototype is still very incipient, that more numerous trials are needed and also longer terms to confirm treatment safety and efficacy. But it does have the potential to become a method to reach more frequent dialysis in patients with advanced kidney failure.

Bioartificial Renal Assist Device (RAD)

Based on the fact that there are a series of progenitor cells that regenerate the tubular epithelium after tubular necrosis or acute kidney failure of any given aetiology, Humes et al.[10] were able to select this type of cell population and make elements similar to tubules in collagen gels with programmed growth factors. They introduced a fixing matrix inside the polysulfone capillary, filling it up with progenitor cells. Culture medium with growth factors was added in the extracapillary space to aid expansion and differentiation of cells until a layer was formed to fill up the capillary inner surface, thus fabricating a bioartificial tubule.

Up to then renal function replacement in case of acute kidney failure succeeded only in replacing the elimination of light-molecular-weight solutes and volume, but without restoring metabolic properties and endocrine kidney functions, which reside in its cellular elements.

This group developed an extracorporeal circulation device with a haemofiltration filter that contains millions of human kidney tubule cells inside the capillary fibres. Preclinical studies showed that these cells retained metabolic and endocrine transport properties in uraemic animals[11] and, additionally, improved multiorganic dysfunction in the septic shock by gram-negatives in a wide series of animals.[12,13]

Tumlin et al.[14] have studied, in a duration no longer than 72 hours, whether treatment with RAD (renal assist device) improves survival in patients with acute kidney failure by comparing it against continuous replacement treatment in a multicentre randomized controlled study affecting 58 patients with acute kidney failure who required dialysis. Forty patients received veno-venous haemofiltration associated with RAD and only 18 continuous renal replacements. The primary objective was mortality to 28 days, and other objectives were mortality to 90 days and to 180 days, renal function recovery time, hospitalisation time at ICU, total hospitalisation time and safety. At day 28, mortality was 33% in the RAD group and 61% in the group that received continuous renal replacement. Improved survival was also found at day 180 in the RAD group with 50% mortality risk with respect to continuous replacement group. Furthermore, under RAD treatment a fast renal function recovery was observed and tolerance improved.

At present, this technological advancement is in preparation at multicentre randomised stage 3 to evaluate its therapeutic effect more consistently, and there are several publications available for the interested reader.[15-19]

PERITONEAL DIALYSIS: VIWAK PD

The Vicenza Wearable Artificial Kidney for Peritoneal Dialysis (ViWAK PD) is an initial prototype that aims at an improved convenience for patients receiving peritoneal dialysis, a technique that, despite being the most important home technique, still faces significant barriers to it, such as daily duration that sets limitations to everyday living.

Ronco et al.[20] have developed the ViWAK PD system with aims at performing out-patient continuous peritoneal dialysis only with some manoeuvres in the morning and evening, thus leaving the patient free during the day and at night. This method consists in: *1)* double-channel peritoneal catheter; *2)* dialysing outlet line; *3)* a small size pump; *4)* a dialysing regeneration circuit with four chambers in parallel with a mix of active carbon and resins; *5)* a filter for microbiologic protection; *6)* an input line for the dialysis liquid, and *7)* a very small computer that is a remote control.

This system provides weekly clearance of 100 to 110 litres and consists in filling up the cavity with 2-litre solution. After two hours there is activation in dialysis liquid recirculation at a speed of 20ml/min during 10 hours. After stopping recirculation, glucose is added if it is necessary to ultrafiltrate and after 2 hours it is emptied and icodextrin is added for the night if necessary. This system may be a possible alternative to either APD or CAPD, as it reduces the time dedicated to exchanges and improves efficacy in the technique and rehabilitation for the patient.

In short, the techniques exposed above are based on the technological evolution of recent years, which have made it possible to reduce both size and weight of the instruments needed. Let us hope that in the future miniaturisation will be able to improve renal function replacement treatment with dialysis by enabling a more continuous treatment and, consequently, a more physiological one. There is of course a very important step left: perfecting vascular access should occupy a place of preference in research, but it is unfortunately far from being so at the moment.

KIDNEY TRANSPLANT

In the context of progress made in treating kidney diseases, we will now discuss xenotransplant and regenerative medicine. Advancement regarding increase in donors' pool, new immuno-suppressants, research over transplanted kidney dysfunction, and especially tolerance in identifying biomarkers indicating whether the patient is or not in a tolerance stage, and in developing strategies to induce tolerance, all these are not included.

Xenotrasplant

Xenotransplant using pigs' kidneys might solve the problem of donor shortage. In the last 20 years much progress has been made regarding immunologic pig/non-human primate mechanisms and we are now close to performing clinical trials.

Outcomes from kidney transplants from pigs to non-human primates earlier than 1998 showed hyper-acute rejection due to the existence of antibodies pre-formed, mainly anti-GAL, an antigenic constituent of the pig's vascular wall that led to complement activation and intravascular coagulation and thrombosis.[21] In the year 2000 a Cambridge group reached up to a 78-day survival for cynomolgus monkeys[22] using transgenic pig kidneys for human complement regulatory proteins (hDAF). Therefore, hyper-acute rejection had been prevented but the graft continued to be lost to acute humoral rejection. It seemed that it was caused by the presence of non-anti-GAL[23] antibodies. However, when acute humoral rejection was prevented the presence of thrombotic microangiopathy and coagulation alterations was more evident.

Future steps to be taken in the study of xenotransplant may be summarised as follows:[24]

1. New immunosuppressant agents.
2. Identification of non-GAL antigens in pigs.
3. Study of disregulation of coagulation between pigs and primates.
4. Resolve the problem of coagulation acting over transgenic pigs with anticoagulation or anti-thrombotic gene or removing pro-coagulation genes.
5. Develop donor-specific tolerance.
6. Improve the study of physiology for some types of organs.
7. Study of cross-species infection (xenozoonosis).
8. Minimise risk of porcine endogenous retrovirus.
9. Consolidate and improve ethical and social regulations.

Regenerative medicine

The kidney has a potential for regeneration through the tubular epithelial cells, which is what in part occurs with acute kidney injury. However, with chronic kidney disease the kidney does not have the self-regulation potential, and complete development of a new kidney becomes necessary.

In order to achieve a regenerated kidney, it is necessary that the techniques applied render a precise structure of the kidney, a kidney that produces urine and grows without the need of immunosuppression.

Four possibilities to achieve a new kidney are discussed below:

1. Embryonic kidney (metanephros)
2. Embryonic stem cells
3. Nuclear transplant
4. Xenogeneic embryos.

Embryonic kidney (metanephros)

Metanephros is the renal precursor that originates during the fifth gestation week in humans or around day 12 in rat's embryonic development.

Rogers et al.[25] implanted rat metanephros in non-immunosuppressed rat's peritoneum. These 15-day metanephros increased in size 6 weeks after implantation, they had also vascularised aided by the contribution of vessels of the receiving rat (absence of hyper-acute rejection), and formed mature tubules and glomeruli. Metanephros ureter was connected to a kidney that was removed and 4 weeks later the contralateral kidney was removed. The kidney transplanted produced urine and the rats so transplanted increased their average life. These results make it reasonable to use metanephros of early embryos as a potential source for the kidney to be regenerated and thus solve the problem of donor shortage. Osafune et al.[26] isolated a particular population of cells from metanephric mesenchyme that were enough to make a complete kidney, which suggest the possibility of creating a kidney from a single stem cell from the metanephric mesenchyme.

Embryonic stem cells

These are undifferentiated pluripotent cells, isolated from the blastocyst inner layer, that have the capacity to differentiate into different cell types: mesodermic, endodermic, and ectodermic, depending on the culture conditions. These include, consequently, cells that have a potential for tissue regeneration. There are no published data that describe the complete process of kidney formation from embryonic stem cells, but several groups have shown that stem cells may differentiate in renal structures when they are injected in immunosuppressed rats.

Some examples will be provided. Along these lines, Vigneau et al.,[27] using a combination of different conditions of culture and selection, and specially pre-differentiating embryonic stem cells *in vitro* toward the desired line, were able to generate a pure population of proximal tubule progenitors capable of integration in normal nephrons without causing teratoma (which is one of the main problems of these techniques). With a simple injection in the kidneys of newborn rats, after 7 months such integration was achieved, although not in glomeruli. However, all these types of cells may cause an immunologic response. Injecting rat mesenchymal stem cells in the kidney, Kunter et al.[28] achieved preservation of renal function in a progressive glomerulonephritis model in rats, but with a long-term complication involving inadequate differentiation of these mesenchymal stem cells in adipocytes accompanied by glomerular sclerosis.

Nuclear transplantation

It consists of the introduction of a donor cell nucleus into a nucleus-free oocyte to generate an embryo with a genetic map similar to that of the donor.

Lanza et al.[29] tried to create a unit that eliminated the problem of the immunologic response. They generated a kidney histocompatible for organ transplantation. They used the nuclear transplant technique, where isolated adult cow dermal fibroblasts were transferred to bovine oocytes introduced in nuclei and implanted in recipients. A renal apparatus full of cloned metanephric cells was transplanted into the cow from which the fibroblasts had been taken. Surprisingly enough, it produced urine, a fact

that point to the possibility of a nuclear transplant for renal regeneration without risk of immunosuppression for the long term.

We are therefore closer to achieving the following ideal events for an artificially regenerated kidney to be possible: precise renal structure, urine production, and immunosuppression-free growth.

Xenogenic embryos as organ factories

During metanephros development, a glial cell line-derived neurotrophic factor (GDNF) is expressed to initiate development. Mesenchymal stem cells expressing GDNF are likely to differentiate themselves in the renal structures provided they are placed in the adequate site.

Yokoo et al.[30,31] injected human mesenchymal stem cells in the site of the metanephros formation. The metanephros were dissected and cultivated afterwards. It was later observed that if mesenchymal cells expressing GDNF were injected, they could generate complete nephrons. However, to achieve a functional nephron it was necessary to have vascular integration and to do so, metanephros were transplanted into rat peritoneum, thus increasing size and developing a renal structure similar to what had previously been published by Roger.[25] Urine was collected from ureters and erithropoietin production was observed.[32] It was concluded that human mesenchymal stem cells might, in the future, replace renal function.

CHRONIC KIDNEY DISEASE

Personally I believe that one of the great advances that will be made in the future is, apart from what has already been said, how we will face chronic kidney disease. Three concepts raise an important discussion here: stop progression, regression of sclerosis and, lastly, humanization and social cost reduction for chronic kidney disease

Stopping progression

Nowadays, in everyday clinical practice, when dealing with a patient with chronic kidney disease the main objective is to stop the disease's progression. There are numerous publications in patients to achieve this objective and, of course, no reference to them will be made in this article that is about future, directions but a summary will be presented on how progression can be stopped[33] with the following measures: arterial pressure control, proteinuria control, diabetes control, blocking renin-angiotensin system, renin inhibition, protein dietary restriction (uncertain), use of statins (to be confirmed), use of paricalcitol (to be confirmed), anaemia control (not clearly demonstrated yet), weight reduction when obesity is present, suppression of tobacco, and prevention of nephrotoxic medication.

Regression

The question of whether chronic kidney disease may regress is of great complexity. Numerous studies in humans have been performed whith only slight reductions in the deterioration of renal function. There is, however, experimental studies that show that regression seems to have been achieved, which probably means that pathogenic mechanisms differ between animals and human beings.

The following factors have been involved in kidney disease progression:

1. Paracrine factors: angiotensin 2, endothelin, growth factors.
2. Metabolic factors: proteinuria, hyperglycaemia, dyslipidaemia, oxidative stress, hypoxia.
3. Genetic factors.
4. Haemodynamic factors: arterial hypertension, glomerular hypertension, *shear stress*.
5. Cellular factors: epithelial mesenchymal transition, myofibroblasts.
6. Inflammatory factors: cytokines, chemokines, *Toll like receptors*.

Of all these, blockage of angiotensin 2 is the target element, the most important to achieving renal fibrosis regression but, in humans, this is not enough.

There are many experimental data in which chronic kidney disease was reverted by suppressing the renin-angiotensin system (RAS). Regardless of whether renal insufficiency was caused by an aging model or by nitric oxide inhibition model, or with nephrectomy, or through diabetes induction; the truth is that in most studies regression was obtained by blocking the RAS mechanism.[38]

Therefore, experimental chronic kidney disease regression achieved in rodents has not been reproduced in humans. In this case angiotensin 2 does play a very important role in the development of kidney disease, due to its multiple actions, independently of hypertension and sodium balance. Angiotensin 2 is part of almost all that is related to vascular diseases and many other actions that are currently being shown every day. This blockage is therefore necessary but, as it has already been mentioned, clinical data point at the fact that it is not enough. It is necessary to carry on in order to identify other additional

target elements and apply treatments to them. Amongst the treatments performed to observe regression of renal lesions the following can be found[33,38]:

1 Anti-inflammatory agents and among them TAK 603, rapamycin or NF kappa beta inhibitor. It seems that inflammation inhibition may be beneficial if performed very early upon developing chronic kidney disease, but for the long term its effect is limited.

2 TGF beta antagonist: it is a factor considered the major activator of extracellular matrix synthesis and, consequently, of fibrosis production. Bone morphogenetic protein 7 (BMP7) or hepatocyte growth factor (HGF) are amongst the agents proposed to block TGF beta fibrogenic action. Other antifibrotic medication that inhibit TGF beta are IN1130 or Tranilast, which inhibits the release of TGF beta from inside cells as fibroblasts and macrophages.

3 Receptors inhibitors of tyrosine kinase growth factor.

4 Inhibitors of intracellular signal such as, for example, inhibitor of p38 MAPK, a protein kinase that has been studied in renal graft chronic nephropathy, or protein kinase C inhibition, that so far has not given results to be assessed.

5 Aldosterone antagonist. It is an important profibrogenic agent in myocardial fibrosis, less known in kidney disease progression, although for the moment data do not confirm this possibility.[39]

6 Activation of kinine receptors and, consequently, inhibition of angiotensin conversion enzyme.

7 Statins: acting independently from cholesterol reduction. Their beneficial action has been demonstrated in some animals; treatment with rosuvastatin has a renoprotective effect in both morphology and inflammation, with reduction of matrix metalloproteinase independently of arterial pressure.[40]

8 Inhibitors of collagen receptors.

9 Agents that degrade the extracellular matrix. There are laboratory data indicating that activation of matrix metalloproteinase plays a beneficial role against renal fibrosis development induced by nitric oxide deficiency.[41]

To conclude, in most studies chronic kidney disease regression was achieved by means of blocking or antagonising RAS action. A list of mediators for profibrogenic actions of angiotensin 2 will probably appear in the future but, in any case, what does seem clear is that if ever any beneficial effect in humans is achieved it will be by starting up a very early treatment, before the disease reaches the point of no return renal insufficiency.

Preservation of endothelial integrity

The kidney has a very important endothelial surface and much attention has recently been given to vascular damage causing ischaemia of renal tissue and progression of chronic kidney disease. Consequently, preserving vascular integrity and that of the endothelial wall not only prevents cardiovascular events associated with chronic kidney disease, but it also constitutes an important point to stopping progression of kidney disease. Endothelial cells of the vascular tree respond to signals such as endocrine or paracrine hormones, cytokines and growth factors, exogenous and endogenous toxins, including traditional and non-traditional vascular risk factors. Meanwhile, the endothelium also responds to rheological and haemodynamic changes. However, amongst all these, oxidative stress and inflammation are the most significant elements causing endothelial and vascular dysfunction in patients with chronic kidney disease.

Although it was believed that damaged endothelial cells were replaced by neighbouring cells being introduced in the injured endothelial area, we now know of endothelial progenitor cells (EPC) that come from haemopoietic stem cells and that contribute to vascular repair and even to vascular regeneration. It is known, based on experimental data, that infusion or injection of endothelial progenitor stem cells improves heart function after myocardial infarction and favours blood flow in peripheral ischaemic models.[42] In theory, these endothelial progenitor cells would favour re-endothelialisation and neovascularisation, although, so far, studies have shown that the capacity to differentiate in renal tissues is very limited, so that other alternatives should be sought to improve vascular repair and regeneration of chronic kidney disease.

Different studies of endothelial progenitor cells in chronic kidney disease have shown that there are abnormalities in number and function in patients, that the capacity for re-endothelisation *in vivo* of these progenitor cells is affected in patients with diabetes type 2, and that this functional reduction in these cells in chronic kidney disease is improved with dialysis and renal transplant.[43-45] There are also pharmacological approaches to improve EPC regenerative capacity in chronic kidney disease. Along these lines, improvement has been shown in the number and functional capacity of the EPC with rosiglitazone in diabetic patients,[46] erythropoietin[47], angiotensin receptor blockers[48] or statins.[49]

Therefore, an attempt to control endothelial damage that associates progression of chronic kidney disease with cardiovascular disease may be done by repair-regeneration through two possibilities: pharmacological treatment to improve deregulation of EPC and cellular

therapy. However, in this field, physiological significance and long-term risks, particularly poor differentiation and inadequate transformation, are not clear at the moment.

Humanization and social cost reduction for chronic kidney disease

In year 2008 around 45,000 people in Spain, specifically, approximately 1,000 people per million, were already undergoing kidney replacement treatment, a figure that is estimated to be doubled in the next 10 years due to progressive ageing of the population and increase in the prevalence of other chronic processes such as diabetes mellitus. The same holds true in the developed world where, although the incidence is gradually stabilising, the prevalence of patients receiving renal function replacement treatment, either by dialysis or renal transplant, continues to advance considerably until reaching figures of 2,200 per million people in Taiwan ¡n 2008 and 1,900 in Japan, or 1,650 in the United States. Such a growth in prevalence is alarming, and it can offset the balance of health services in some countries in the future.[50]

As it happens in the rest of the developed countries, the population starting on dialysis is ageing remarkably in Spain. Along these lines, according to the Spanish registry of renal patients in the year 2007, with an incident population of mean 125/million, the number of patients over 75 years was 405/million.[51] Many of these cases older than 75 years of age present with three or more co-morbidities and their life expectation is very low. An ethical question has to be bravely asked: Is dialysis for everyone?

In developed countries there are currently no limitations to apply renal replacement treatment. Frequently, this situation leads to not assessing adequately each single treatment for each particular patient and, however, it is evident that not all patients benefit equally from this treatment. We are faced with ethical reflections that are very important for us to discuss with our patients and their families, that fortunately in Spain they can be found in our journal NEFROLOGÍA.[52-54] Some studies that analyse survival in patients older than 75, retrospectively, in pre-dialysis clinics with chronic kidney disease stage 5 find that the advantage of undergoing dialysis is significantly reduced by co-morbidity and by ischaemic heart disease in particular.[55] An indeed practical approach to this issue is that by Couchoud et al.[56] who, with a simple rating of co-morbidities, draw the short-term prognosis in patients older than 75 starting on dialysis. This can help making a rational clinical decision when discussing with patients and their families. A clinical score of CKD patients to take decisions is also a direction for the future of chronic kidney diseases.

REFERENCES

1. US Renal Data System. Available at: http:/// http://www.usrds.org/
2. Kjellstrand CM, Evans RL, Petersen RJ, et al. The «unphysiology» of dialysis: A major cause of dialysis side effects? Kidney Int 1975;(Supl 2):30-4.
3. Nissenson AR, Ronco C, Pergamit G, et al. The human nephron filter: Continuously functioning, implantable artificial nephron system. Blood Purif 2006;23:269-74.
4. Nissenson AR, Ronco C, Pergamit G, et al. Continuously functioning artificial nephron system: The promise of nanotechnology. Hemodial Int 2005;9:210-7.
5. Leonard EF, West AC, Shapley NC, Larsen MU. Dialysis without membranes: How and why? Blood Purif 2004;22:92-100.
6. Leonard EF, Cortell S, Vitale NG. Membraneless dialysi-is it possible? Contrib Nephrol 2005;149:343-53.
7. Gura V, Beiza M, Ezon C, Polaschegg HD. Continuous renal replacement therapy for end-stage renal disease: the wearable artificial kidney (WAK). Contrib Nephrol 2005;149:325-33.
8. Gura V, Beizai M, Ezon C, Rambod E. Continuous renal replacement therapy for congestive heart failure: the wearable continuous ultrafiltration system. Am Soc Artif Inter Organs J 2006;52:59-61.
9. Davenport A, Gura V, Ronco C, Beizai M, Ezon C, Rambod E. A wearable haemodialysis device for patients with end-stage renal failure: a pilot study. Lancet 2007;370:2005-10.
10. Humes HD, MacKay SM, Funke AJ, Buffington DA. Tissue engineering of a bioartificial renal tubule assist device: in vitro transport and metabolic characteristics. Kidney Int 1999;55(6):2502-14.
11. Humes HD, Buffington DA, MacKay SM, Funke AJ, Weitzel WF. Replacement of renal function in uremic animals with a tissue-engineered kidney. Nat Biotechnol 1999;17(5):451-5.
12. Fissell WH, Lou L, Abrishami S, Buffington DA, Humes HD. Bioartificial kidney ameliorates gram-negative bacteria-induced septic shock in uremic animals. J Am Soc Nephrol 2003;14(2):454-61.
13. Humes HD, Buffington DA, Lou L, et al. Cell therapy with a tissue-engineered kidney reduces the multipleorgan consequences of septic shock. Crit Care Med 2003;31:2421-8.
14. Tumlin J, Wali R, Williams W, et al. Efficacy and safety of renal tubule cell therapy for acute renal failure. J Am Soc Nephrol 2008;19(5):1034-40.
15. Humes HD, Fissell WH, Weitzel WF, et al. Metabolic replacement of kidney function in uremic animals with a bioartificial kidney containing human cells. Am J Kidney Dis 2002;39:1078-87.
16. Tiranathanagul K, Eiam-Ong S, Humes HD. The future of renal support: High-flux dialysis to bioartificial kidneys. Crit Care Clin 2005;21:379-94.
17. Humes HD, Weitzel WF, Bartlett RH, et al. Initial clinical results of the bioartificial kidney containing human cells in ICU patients with acute renal failure. Kidney Int 2004;66:1578-88.
18. Humes HD, Weitzel WF, Fissell WH. Renal cell therapy in the treatment of patients with acute and chronic renal failure.

Blood Purif 2004;22:60-72.
19. Fissell WH, Dyke DB, Weitzel WF, et al. Bioartificial kidney alters cytokine response and hemodynamics in endotoxin-challenged uremic animals. Blood Purif 2002;20:55-60.
20. Ronco C, Fecondini L. The Vicenza wearable artificial kidney for peritoneal dialysis (ViWAK PD). Blood Purif 2007;25:383-8.
21. Shimizu A, Yamada K. Pathology of renal xenograft rejection in pig to non-human primate transplantation. Clin Transplant 2006;20(Suppl 15):46-52.
22. Cozzi E, Bhatti F, Schmoeckel M, Chavez G, Smith KG, Zaidi A, et al. Long-term survival of non-human primates receiving life-supporting transgenic porcine kidney xenografts. Transplantation 2000;70:15-21.
23. Chen G, Sun H, Yang H, Kubelik D, Garcia B, Luo Y, et al. The role of anti-non-GAL antibodies in the development of acute humoral xenograft rejection of hDAF transgenic porcine kidneys in baboons receiving anti-gal antibody neutralization therapy. Transplantation 2006;81:273-83.
24. Ekser B, Rigotti P, Gridelli B, Cooper DK. Xenotransplantation of solid organs in the pig-to-primate model. Transpl Immunol 2009;21(2):87-92.
25. Rogers S, Lowell JA, Hammerman NA, Hammerman MR. Transplantation of developing metanephroi into adult rats. Kidney Int 1998;54:27-37.
26. Osafune K, Takasato M, Kispert A, Asashima M, Nishinakamura R. Identification of multipotent progenitors in the embryonic mouse kidney by a novel colony-forming assay. Development 2005;133:151-61.
27. Vigneau C, Polgar K, Striker G, et al. Mouse embryonic stem cell-derived embryoid bodies generate progenitors that integrate long-term into renal proximal tubules in vivo. J Am Soc Nephrol 2007;18:1709-20.
28. Kunter U, Rong S, Boor P, et al. Mesenchymal stem cells prevent progressive experimental renal failure but maldifferentiate into glomerular adipocytes. J Am Soc Nephrol 2007;18(6):1754-64.
29. Lanza RP, Chung HY, Yoo JJ, et al. Generation of histocompatible tissues using nuclear transplantation. Nat Biotech 2002;20:689-96.
30. Yokoo T, Ohashi T, Shen JS, et al. Human mesenchymal stem cells in rodent whole-embryo culture are reprogrammed to contribute to kidney tissues. Proc Natl Acad Sci USA 2005;102:3296-300.
31. Yokoo T, Fukui A, Ohashi T, et al. Xenobiotic kidney organogenesis from human mesenchymal stem cells using a growing rodent embryo. J Am Soc Nephrol 2006;17:1026-34.
32. Yokoo T, Fukui A, Matsumoto K, et al. Generation of transplantable erythropoietin-producer derived from human mesenchymal stem cells. Transplantation 2008;85:1654-8.
33. Hsu C, Schieppati A. Chronic Kidney Disease and Progresion. ASN: Nephrology Self-Assessment Program, 2006;5:6.
34. Vilayur E, Harris DC. Emerging therapies for chronic kidney disease: what is their role? Nat Rev Nephrol 2009;5(7):375-83.
35. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851-60.
36. Brenner BM, Cooper ME, De Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345:861-9.
37. Parving HH, Lehnert H, Brochner-Mortensen J, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 2001;345:870-8.
38. Chatziantoniou C, Dussaule JC. Is kidney injury a reversible process? Curr Opin Nephrol 2008;17:76-81.
39. Kramer AB, Van der Meulen EF, Hamming I, et al. Effect of combining ACE inhibition with aldosterone blockade on proteinuria and renal damage in experimental nephrosis. Kidney Int 2007;71:417-24.
40. Gianella A, Nobili E, Abbate M, et al. Rosuvastatin treatment prevents progressive kidney inflammation and fibrosis in stroke-prone rats. Am J Pathol 2007;170:1165-77.
41. Boffa JJ, Ying L, Placier S, et al. Regression of renal vascular and glomerular fibrosis: Role of angiotensin II receptor antagonism and metalloproteinases. J Am Soc Nephrol 2003;14:1132-44.
42. Schachinger V, Erbs S, Elsasser A, et al. Intracoronary bone marrow derived progenitor cells in acute myocardial infarction. N Engl J Med 2006;355:1210-21.
43. De Groot K, Bahlmann FH, Sowa J, et al. Uremia causes endothelial progenitor cell deficiency. Kidney Int 2004;66:641-6.
44. De Groot K, Bahlmann FH, Bahlmann E, et al. Kidney graft function determines endothelial progenitor cell number in renal transplant recipients. Transplantation 2005;79:941-5.
45. Schlieper G, Hristov M, Brandenburg V, et al. Predictors of low circulating endothelial progenitor cell numbers in haemodialysis patients. Nephrol Dial Transplant 2008;23:261-8.
46. Sorrentino SA, Bahlmann FH, Besler C, et al. Oxidant stress impairs in vivo reendothelialization capacity of endothelial progenitor cells from patients with type 2 diabetes mellitus: restoration by the peroxisome proliferator-activated receptor-gamma agonist rosiglitazone. Circulation 2007;116:163-73.
47. Bahlmann FH, De Groot K, Spandau JM, et al. Erythropoietin regulates endothelial progenitor cells. Blood 2004;103:921-6.
48. Bahlmann FH, De Groot K, Mueller O, et al. Stimulation of endothelial progenitor cells: a new putative therapeutic effect of angiotensin II receptor antagonists. Hypertension 2005;45:526-9.
49. Landmesser U, Bahlmann F, Mueller M, et al. Simvastatin versus ezetimibe: pleiotropic and lipid-lowering effects on endothelial function in humans. Circulation 2005;111:2356-63.
50. Lysaght MJ. Maintenance dialysis population dynamics: current trends and long-term implications. J Am Soc Nephrol 2002;13(Suppl 1):S37-40.
51. http://www.senefro.org/
52. Sánchez Tomero JA. Planificación anticipada e inicio de diálisis. Nefrologia 2009;29(4):285-7.
53. Sarrías Lorenz X, Bardón Otero E, Vila Paz ML. El paciente en prediálisis: toma de decisiones y libre elección terapéutica. Nefrologia 2008;28(3):119-22.
54. Tejedor A, De las Cuevas X. Cuidado paliativo en el paciente con enfermedad renal crónica avanzada (grado 5) no susceptible de

tratamiento dialítico. Nefrologia 2008;28(3):123-5.
55. Murtagh FE, Marsh JE, Donohoe P, et al. Dialysis or not? A comparative survival study of patients over 75 years with chronic kidney disease stage 5. Nephrol Dial Transplant 2007;22(7):1955-62.
56. Couchoud C, Labeeuw M, Moranne O, et al, French Renal Epidemiology and Information Network (REIN) registry. A clinical score to predict 6-month prognosis in elderly patients starting dialysis for end-stage renal disease. Nephrol Dial Transplant 2009;24(5):1553-61.